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Description

BACKGROUND OF THE INVENTION

This invention relates to a novel process for preparing d-α-(6-methoxy-2-naphthyl)propionic acid.

The d-α-(6-methoxy-2-naphthyl)propionic acid or its salt is useful as, for example, anti-flammatory or analgesic agents.

As processes for preparing d-α-(6-methoxy-2-naphthyl)propionic acid, there have been heretofore known (i) a process in which racemic modification of α-(6-methoxy-2-naphthyl)propionic acid as optically resolved, (ii) a process in which an ester of d-α-(6-methoxy-2-naphthyl)propionic acid is hydrolyzed in the presence of an acid catalyst, and the like.

The process in which racemic modification of α-(6-methoxy-2-naphthyl)propionic acid is optically resolved, however, can not be said to be a satisfactory one from an economical view point because it is necessary to repeat the crystallization several times or more and to use expensive agents for the optical resolution.

In the process in which an ester of d-α-(6-methoxy-2-naphthyl)propionic acid is hydrolyzed in the presence of an acid catalyst, the methoxy group at the 6-position in the naphthyl group of the carboxylic acid which is a desired product or of the unreacted starting ester tends to be partially converted to a hydroxy group by hydrolysis to form d-α-(6-hydroxy-2-naphthyl)propionic acid or its ester as a by-product, requiring treatment for purification after completion of the hydrolysis, and therefore the above process also can not be said to be a fully satisfactory one for an industrial application.

Further, there is known a process in which an ester of d-α-(6-methoxy-2-naphthyl)propionic acid is hydrolyzed in an organic solvent containing an alkali catalyst. In this process, however, racemization reaction occurs simultaneously with hydrolysis to result in remarkable decrease in the optical purity of the resulting product (see U.S. Patent No. 4,417,070, Table 2 on page 4), and the process can be said not to be of a good efficiency.

SUMMARY OF THE INVENTION

The present inventors have made extensive studies in order to eliminate the drawbacks in the processes described above, and as a result, have found a fact that a process in which the hydrolysis is effected in an aqueous alkali catalyst solution is unexpectedly accompanied with little racemization reaction, and have accomplished this invention.

More specifically, in hydrolysing an ester such as the ester of d-α-(6-methoxy-2-naphthyl)propionic acid, which is hardly soluble in water, there have been usually used water-soluble organic solvents such as ethanol, methanol and the like, which are capable of dissolving the ester of d-α-(6-methoxy-2-naphthyl)-propionic acid but do not participate in the reaction, in order to enhance the rate of reaction.

Opposed to the above, the present inventors have used water as a solvent, and as a result, have found that hydrolysis of the ester group unexpectedly proceeds while remarkably suppressing the racemization, and have accomplished this invention.

The present inventors have further found that in the present process there does not occur a side reaction that the methoxy group at the 6-position on the naphthyl group of the carboxylic acid or of the unreacted starting ester is converted to a hydroxy group by hydrolysis to form a by-product d-α-(6-hydroxy-2-naphthyl)propionic acid or its ester, whereas such a side reaction is observed in the acid-catalyzed hydrolysis as mentioned above.

Accordingly, this invention is to provide a novel process for preparing d-α-(6-methoxy-2-naphthyl)-propionic acid, which is characterized by hydrolyzing an ester of d-α-(6-methoxy-2-naphthyl)propionic acid in an aqueous alkali catalyst solution.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention will be described in more detail below.

The ester of d-α-(6-methoxy-2-naphthyl)propionic acid which is used as a starting material may be a lower alkyl ester excluding t-butyl ester of said acid, or an ester of said acid with a phenyl group unsubstituted or substituted with an electron attracting group such as Cl, NO_2 and Br, preferably methyl ester or ethyl ester, and most preferably methyl ester.

The alkali catalyst to be used in this invention includes, for example, an alkali hydroxide such as sodium hydroxide, potassium hydroxide and lithium hydroxide; ammonia; an alkali metal carbonate such as sodium carbonate and potassium carbonate; an alkali metal bicarbonate such as sodium bicarbonate and potassium bicarbonate; an alkali metal salt of an organic acid such as sodium acetate and potassium acetate, a salt of d-α-(6-methoxy-2-naphthyl)propionic acid or α-(6-methoxy-2-naphthyl)propionic acid such as potassium, sodium and amonium salt of said acid, and the like.

The concentration of the alkali catalyst in the aqueous solution may be in the range from 0.01 to 40%, preferably from 0.1 to 25%. The higher the concentration of the solution is, the faster the reaction proceeds.

The reaction temperature may be in the range from 0°C to a temperature at which the reaction solution is refluxed, i.e., from 0°C to 100°C.

With respect to the ratio of the ester of d-α-(6-methoxy-2-naphthyl)propionic acid which is used as a starting material to the water which is used as a solvent (ester/water), the smaller the ratio is, the faster the

reaction proceeds. On the contrary, the greater the ratio is, the higher volumetric efficiency is.

The ratio may be usually in the range from 10 to 0.001, preferably 1.0 to 0.001.

The reaction time is not limitative so long as it is enough to carry out the reaction completely and maintains the degree of retention of the configuration in an asymmetric carbon of the product at the desired level or higher. Although the desired reaction time may be varied depending upon the degree of optical purity to be maintained or the concentrations of the alkali catalyst and/or the substrate (ester), it may be usually in the range from approximately 30 minutes to 100 hours. It is possible to shorten or extend, the reaction time to any degree depending upon the desired degrees of optical purity and hydrolysis or the reaction conditions.

As the hydrolysis reaction proceeds, an alcohol is produced from the ester group of the starting ester. An aqueous alkali catalyst solution containing the alcohol thus produced or an alcohol in a ratio (by weight or by volume) corresponding to that of the alcohol thus produced is included in the "aqueous alkali catalyst solution" defined in this invention.

The process according to this invention will be described in more detail by the following Examples and Comparative Example.

Example 1

1 g of methyl ester of d-α-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D^{25}$ +78.7° (c = 1, Chloroform); optical purity 100%) suspended in 40 g of 1% aqueous potassium carbonate solution was heated at 100°C for 6 hours and then cooled. To the resulting reaction mixture, 10 ml of toluene and 5 ml of 5% aqueous sodium hydroxide solution were added to conduct partition. The aqueous layer was neutralized with hydrochloric acid and a solid deposited was extracted with 10 ml of ethyl acetate. After the organic layer was washed with water, concentrated by distilling the solvent away and dried to obtain 0.72 g of white crystal of d-α-(6-methoxy-2-naphthyl)propionic acid. Yield: 76%; $[\alpha]_D^{25}$ +64.8° (c = 1.0, Chloroform); optical purity 94%.

Comparative Example 1

(a conventionally available process utilizing alkali-catalyzed hydrolysis)

After 2.3 g of ethyl ester of d-α-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D^{25}$ +48.6°; optical purity 100%), 7.3 g of ethanol, 2.5 g of water and 0.5 g of sodium hydroxide were combined, the resulting reaction mixture was heated under reflux for 4 hours, cooled, acidified with hydrochloric acid and thereafter partitioned between water and toluene. The toluene layer thus obtained was washed with water and concentrated to obtain 1.9 g of d-α-(6-methoxy-2-naphthyl)propionic acid. The optical purity was 45%.

Examples 2 to 8

Experiments for Examples 2 to 8 were carried out under the same reaction conditions and post treatment conditions as in Example 1 except that the kinds of the ester of d-α-(6-methoxy-2-naphthyl)-propionic acid and the alkali catalyst to be used, reaction time and reaction temperature were varied. The rsults are shown in the following Table. In the experiments for Examples 2 to 8, used were 1 g of the ester of d-α-(6-methoxy-2-naphthyl)propionic acid and 40 g of the aqueous alkali catalyst solution.

Table

Example No.	Ester	Aqueous Alkali catalyst Solution	Reaction conditions Temperature (°C)	Time (hr)	Conversion (%)	Degree of retention of optical activity in carboxylic acid(%)
2	Methyl	0.1%NaOH	100	8	25	93
3	Methyl	25%NaOH	20 - 25	6	8	93
4	Methyl	5%Na_2CO_3	100	4	99	89
5	Ethyl	3%$NaHCO_3$	100	16	31	90
6	Methyl	1%NH_3	100	6	27	91
7	Methyl	1%K_2CO_3	100	6	76	94
8*	Methyl	5%K_2CO_3	100	7	39	94

* For this Example only, the ester and the aqueous alkali catalyst solution as starting material were used in an amount of 1g and 4 g, respectively.

Claims

1. A process for preparing d-α-(6-methoxy-2-naphthyl)propionic acid, by hydrolysis of an ester of d-α-(6-methoxy-2-naphthyl)propionic acid with a basic catalyst characterized in that said hydrolysis is carried out under aqueous conditions.

2. A process according to Claim 1, characterized in that the ester is derived from a lower alkanol having 1 to 3 carbon atoms.

3. A process according to Claim 2, characterized in that the lower alkanol is methanol or ethanol.

4. A process according to any preceding claim, characterized in that the basic catalyst is an alkali metal hydroxide, an alkali metal carbonate, an alkali metal bicarbonate, an alkali metal acetate or a salt of d-α-(6-methoxy-2-naphthyl)propionic acid.

5. A process according to Claim 4, characterized in that the basic catalyst is sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate or potassium bicarbonate.

6. A process according to any preceding claim, the concentration of the basic catalyst in the aqueous solution is in the range from 0.01 to 40% by weight.

7. A process according to Claim 6, characterized in that the concentration is in the range from 0.1 to 25% by weight.

8. A process according to any preceding claim characterized in that the hydrolysis is carried out at a temperature from 0 to 100°C.

Patentansprüche

1. Verfahren zum Herstellen einer d-alpha-(6-Methoxy-2-naphthyl)-Propionsäure durch Hydrolyse eines Esters von d-alpha-(6-Methoxy-2-naphthyl)-Propionsäure mit einem basischen Katalysator, dadurch gekennzeichnet, daß die Hydrolyse unter wässerigen Bedingungen durchgeführt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß der Ester von einem niedrigen Alkanol mit 1—3 Kohlenstoffatomen abgeleitet wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das niedere Alkanol Methanol oder Äthanol ist.

4. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der basische Katalysator ein Alkalimetall-Hydroxid, ein Alkalimetallkarbonat, ein Alkalimetallbikarbonat, ein Alkalimetallacetat oder ein Salz einer d-alpha-(6-Methoxy-2-naphthyl)-Propionsäure ist.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß der basische Katalysator Natriumhydroxyd, Kaliumhydroxyd, Natriumkarbonat, Kaliumkarbonat, Natriumbikarbonat oder Kaliumbikarbonat ist.

6. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Konzentration des basischen Katalysators in der wässerigen Lösung im Bereich von 0,01—40 Gewichts-Prozent liegt.

7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß die Konzentration im Bereich von 0,1—25 Gewichts-Prozent liegt.

8. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Hydrolyse bei einer Temperatur zwischen 0 und 100°C durchgeführt wird.

Revendications

1. Procédé de préparation d'acide d-α-(6-méthoxy-2-naphtyl)propionique par hydrolyse d'un ester de l'acide d-α-(6-méthoxy-2-naphtyl)propionique avec un catalyseur basique, caractérisé en ce que la dite hydrolyse a lieu en milieu aqueux.

2. Procédé selon la revendication 1, caractérisé en ce que l'ester est un dérivé d'un alcanol inférieur contenant de 1 à 3 atomes de carbone.

3. Procédé selon la revendication 2, caractérisé en ce que l'alcanol inférieur est du méthanol ou de l'éthanol.

4. Procédé selon l'une des revendications 1 à 3, caractérisé en ce que la catalyseur basique est un hydroxyde de métal alcalin, un carbonate de métal alcalin, un bicarbonate de métal alcalin, un acétate de métal alcalin ou un sel d'acide d-α-(6-méthoxy-2-naphtyl)propionique.

5. Procédé selon la revendication 4, caractérisé en ce que le catalyseur basique est de l'hydroxyde de sodium, de l'hydroxyde de potassium, du carbonate de sodium, du carbonate de potassium, du bicarbonate de sodium ou du bicarbonate de potassium.

6. Procédé selon l'une quelconque des revendications 1 à 5, caractérisé en ce que la concentration du catalyseur basique dans la solution aqueuse est de l'ordre de 0,01 à 40% en poids.

7. Procédé selon la revendication 6, caractérisé en ce que la concentration est de l'ordre de 0,1 à 25% en poids.

8. Procédé selon l'une des revendications 1 à 7, caractérisé en ce que l'hydrolyse a lieu a une température de 0 à 100°C.